Alerts, Notices, and Case Reports

Fulminant Hepatic Failure Following Low-Dose Sustained-Release Niacin Therapy in Hospital

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NIACIN HAS GAINED wide use as an effective, relatively inexpensive therapy for hypercholesterolemia. Toxic hepatitis due to the use of this drug is rare, poorly understood, and observed more frequently with higher doses (more than 3 grams daily).[1] Sustained-release preparations have gained popularity because of less discomfort from flushing and pruritus. Unfortunately, their use has been associated with increased hepatotoxicity.[1-3] Heightened vulnerability of the liver to the effects of sustained-release (SR) niacin associated with illness or other medications has not been reported. We report the case of a patient, admitted to hospital for a respiratory illness, in whom unexplained fulminant hepatic failure developed following treatment with 2 grams a day of niacin. Although niacin-induced hepatic toxicity is well described, this is the first report of a fatality associated with low-dose SR niacin therapy.

Report of a Case

The patient, a 56-year-old man with emphysema, started taking SR niacin (United Research Laboratories, Philadelphia, Pa), 250 mg twice a day, in January 1989 for the treatment of hypercholesterolemia (7.11 mmol per liter [275 mg per dl]) after dietary modifications had failed. His dose was increased in June 1989 to 1 gram twice a day. The values of serum aspartate aminotransferase (AST) and alkaline phosphatase were normal before he began taking SR niacin, and there was no previous history of infectious hepatitis, jaundice, blood transfusions, substantial alcohol use, known exposure to hepatotoxins, or the use of illicit drugs.

He was admitted to the hospital in October 1989 for the treatment of bronchospasm with cough and hypoxia due to an upper respiratory tract infection and possible pneumonia. He did not have abdominal pain, nausea, or vomiting. In addition to niacin, his medications before admission were metaproterenol sulfate and triamcinolone acetonide inhalers for bronchospasm and clotrimazole and hydrocortisone 1% creams for a chronic rash on his hands and legs. Although he said that he was taking the niacin as prescribed (1 gram twice a day), later review of his unused medications indicated that he may have been taking only half of the prescribed dosage.

On physical examination, the patient was afebrile and had mild tachypnea with decreased breath sounds. An abdominal examination revealed no tenderness or organomegaly. Laboratory values were notable for the following: leukocyte count 9.0×10^9 per liter, hemoglobin 140 grams per liter, PaO_2 40.5 mm of mercury, cholesterol 4.74 mmol per liter (183 mg per dl), and normal electrolytes. Liver function tests were not done on his admission to the hospital. Methylprednisolone sodium succinate, a combination of ampicillin sodium and sulbactam sodium, sucralfate, and heparin prophylaxis were added to his regimen of bronchodilators and SR niacin, 2 grams daily.

The patient's respiratory symptoms waxed and waned over the first five hospital days with gradual improvement in oxygenation and normal oral food intake. On the fifth hospital day, he complained of burning epigastric pain. On rectal examination, his stool was guaiac-positive. Steroid therapy was discontinued, and ranitidine was added. On the sixth hospital day, icterus, right upper quadrant pain, and emesis developed. Oral medication therapy including niacin was discontinued. On the seventh hospital day, liver function test results were abnormal, with an alkaline phosphatase level of 4.5 μmol per liter (270 units per liter), bilirubin 103 μmol per liter (6.0 mg per dl), aspartate aminotransferase (AST)

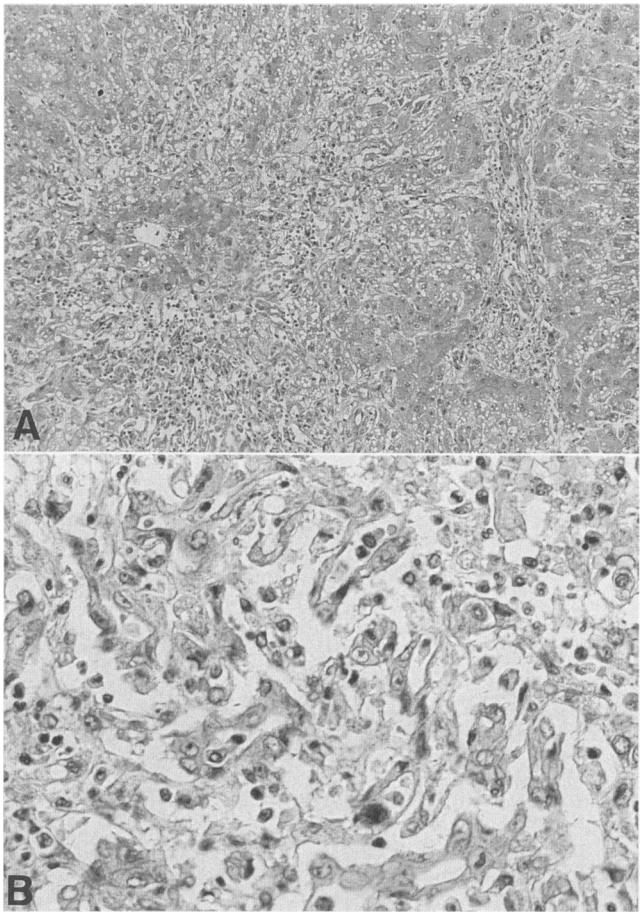

Figure 1.—A, Hepatic damage is most severe through the midzonal area, where necrotic hepatocytes are intermingled with neutrophils and macrophages. Damage is most severe through paracentral and midzonal areas. Small zones of less altered parenchyma occupy a periportal location (original magnification × 100). **B,** A higher power (× 400) view shows extensive vacuolization of hepatocytes.

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ABBREVIATIONS USED IN TEXT
ALT = alanine aminotransferase
AST = aspartate aminotransferase
SR = sustained release

10.90 μkat per liter (654 units per liter), and alanine aminotransferase (ALT) 13.90 μkat per liter (834 units per liter). Abdominal ultrasonography and abdominal computed tomography revealed no obstruction of the biliary architecture and no parenchymal abnormalities. On the eighth hospital day, a coagulopathy and stage I encephalopathy developed with liver enzyme levels peaking at an AST of 33.5 μkat per liter (2,010 units per liter) and an ALT of 42.8 μkat per liter (2,567 units per liter). Tests for hepatitis A antibody (immunoglobulin M) and hepatitis B surface antigen were negative. The patient's clinical condition deteriorated rapidly, with worsening encephalopathy and the development of upper gastrointestinal bleeding. Transplantation was considered but not pursued because of severe underlying emphysema—a forced expiratory volume in one second of 0.51 liters versus a forced vital capacity of 1.7 liters. He was vigorously treated in the intensive care unit with lactulose, fresh frozen plasma, packed erythrocytes, and cryoprecipitate. On the tenth hospital day, the patient died.

An autopsy confirmed the underlying clinical diagnosis of chronic pulmonary emphysema. Coronary and aortic arteriosclerosis and diverticulosis coli were noted. There were ascites, peripheral edema, and pulmonary hyperemia with bilateral pleural effusion. Pneumonic consolidation, infarction, or tumors were not observed. Superficial erosions were noted on examination of the gastric mucosa. The liver weighed 1,000 grams. Cystic and common bile ducts were patent and of normal caliber. On microscopic examination of sections of liver, there was acute hepatic necrosis with prominent fine vacuolization of hepatocytes accompanied by bile stasis. There were some areas of preserved lobular architecture and other areas of complete lobular devastation (Figure 1). Damage was most severe in the paracentral and midzonal areas.

Discussion

The admission history and physical examination and the subsequent hospital course suggest that the hepatotoxic insult occurred after admission to the hospital. Medications other than niacin could have contributed, but there are no specific reports linking methylprednisolone, ampicillin-sulbactam, sucralfate, or heparin to severe hepatotoxicity. Although ranitidine use rarely causes liver injury, it is an unlikely cause in view of the appearance of jaundice the day after ranitidine therapy was begun. Infectious causes including hepatitis B or C are also possible, but hepatitis A and B serologic tests were negative. Although a serologic test for hepatitis C was not available at the time of this patient's admission to hospital, he had no risk factors for hepatitis C. There was also no history of alcohol abuse. Furthermore, the liver did not have the pattern of viral hepatitis or alcohol-induced hepatitis. Its histologic features were typical of niacin-induced hepatic injury.[4] A unique histologic feature in this patient is the paracentral and midzonal localization of the liver injury. This was not noted in a previous report of fulminant hepatic failure.[1] The patient did not receive acetaminophen, and other hepatotoxins are unlikely in the supervised environment of the hospital. Finally, the patient did not have clinical evidence of heart failure or hypotension as a cause for ischemic hepatitis.

The actions of niacin on the liver resulting in decreased cholesterol and triglyceride levels are not understood, nor is the mechanism of hepatotoxicity. Although reports of hepatotoxicity induced by niacin use have appeared sporadically since 1959, with increased enthusiasm for lipoprotein modification, the use of niacin has increased along with reports of toxicity. Most reported cases involve hypercholesterolemic patients treated with crystalline niacin in doses of 4 to 4.5 grams daily, usually for several months.[5] In these reports, the clinical picture was typical of hepatitis with jaundice, pruritus, malaise, hepatomegaly, and mild to moderate elevations of serum bilirubin, alkaline phosphatase, and aminotransferase levels. After the withdrawal of niacin, symptoms usually resolved within a week and biochemical abnormalities resolved within a month. The histologic changes of acute toxic effects are also reversible as occurred in a patient taking 4.5 grams of niacin per day whose hepatitis recurred after rechallenge. The initial liver biopsy showed both massive and submassive lobular collapse, increased fibrosis in some areas of collapse, pronounced cholestasis with canalicular bile plugging, and vacuolated cytoplasm in many hepatocytes.[5] A second liver biopsy done 14 months after the initial one revealed normal architecture.

Although SR niacin is generally thought to be more hepatotoxic than crystalline preparations, it is unknown whether the increased toxicity is due to different local effects on liver cells, a longer exposure time with higher local concentrations, or different absorption characteristics. Three patients who had previous SR niacin-induced hepatitis with equal or higher doses of crystalline niacin reported no evidence of recurring hepatocellular damage, suggesting that the effects of these two preparations may differ substantially.[3] Our patient received SR niacin capsules containing coated pellets that release niacin at progressively longer intervals, depending on the thickness of the coating. It is not known whether a constituent of the SR formulation contributes to the liver injury.

Fulminant hepatic failure associated with SR niacin is poorly characterized and can occur in a variety of clinical circumstances. Mullin and co-workers described the case of a patient who tolerated 6 grams of crystalline niacin daily but in whom fulminant hepatic failure developed three days after an unintentional switch to an SR preparation; the patient required liver transplantation.[1] Hodis recently reported fulminant hepatic failure in an otherwise healthy 32-year-old patient taking 500 mg of SR niacin daily for eight weeks.[6] This patient survived hepatic coma. Our patient had tolerated SR niacin use for four months before admission, with the occurrence of fatal hepatic failure seven days after an increase in dosage from 1 gram to 2 grams daily (assuming he was taking only half of his prescribed dose at home). Whether his acute respiratory illness or other unidentified aspects of his hospital care contributed to the severity of his hepatic failure is unclear.

These recent reports emphasize the need for clinicians to remain alert to the possibility of serious liver dysfunction in any patient taking niacin. Our experience suggests that patients admitted to hospital for any reason who take niacin should be questioned regarding current usage and observed closely for liver function abnormalities or gastrointestinal

complaints. In addition, because SR niacin may be more hepatotoxic in certain patients, its use probably should be restricted to those patients who cannot tolerate the side effects from crystalline niacin formulations.

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Gastric Tuberculosis Presenting as Fever of Unknown Origin

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WHILE THE INCIDENCE of pulmonary tuberculosis has been gradually declining over the past 50 years, that of extrapulmonary tuberculosis has remained relatively constant, and it accounts for almost 20% of all tuberculosis cases.[1,2] Clinically evident tuberculosis of the stomach is rare and is usually associated with concurrent lung infection.[3,4] Cases of isolated gastric tuberculosis without evidence of pulmonary involvement have been reported sporadically.[4] An awareness of these atypical presentations of tuberculosis is necessary for the proper diagnosis and prompt institution of therapy.[5,6] Herein we describe a case of a 74-year-old man with isolated gastric tuberculosis who presented with fever of unknown origin and weight loss. We take this opportunity to review the literature on this disorder, making particular reference to the case discussed here.

Report of a Case

The patient, a 74-year-old man from Nicaragua, was admitted for the evaluation of daily spiking fevers, epigastric pain, and a 9-kg weight loss over the previous three months. He did not have cough, shortness of breath, or a change in bowel habits. The patient had been healthy previously and denied any knowledge of previous tuberculin skin tests. He was married with a single sexual partner and had emigrated from Nicaragua 30 years ago. He had not traveled recently. On admission he was afebrile with normal vital signs. There was no palpable lymphadenopathy, the findings of a cardiac examination were benign, and his lungs were clear. The abdomen was soft with mild epigastric tenderness, and there was no hepatosplenomegaly. An examination of the stool was negative for occult blood. Laboratory values were as follows: urinalysis normal, hematocrit 0.31 (31%), and leukocyte count 13×10^9 per liter (13,000 per μl) with 0.62 (62%) neutrophils, 0.23 (23%) band forms, and 0.06 (6%) lymphocytes. The erythrocyte sedimentation rate (Westergren) was 118 mm per hour. Alkaline phosphatase was 147 U per liter, alanine aminotransferase 31 U per liter, aspartate aminotransferase 41 U per liter, and γ-glutamyl transferase 441 U per liter. A chest radiograph was normal.

During his hospital stay, the patient continued to have daily fevers, with temperatures exceeding 38.5° C (101.3° F) despite antipyretic therapy. The evaluation included multiple cultures of blood, sputum, urine, and stool specimens, all of which were negative for pathogens. An intermediate tuberculin skin test was positive with 15 mm of induration. A bone marrow biopsy was normal, and a liver biopsy revealed nonspecific acute and chronic inflammation. Cultures of bone marrow and liver were negative for bacteria, fungi, and mycobacteria. A computed tomographic (CT) scan of the chest and abdomen revealed a 4- by 4- by 3-cm submucosal mass at the gastroesophageal junction. A mucosal biopsy of the gastric mass revealed acute and chronic gastritis. A second biopsy showed submucosal ulceration and necrotizing granulomas adjacent to lymphoid follicles with germinal center formation. Stains for fungi and acid-fast bacilli were negative.

Antituberculous therapy with isoniazid, rifampin, and pyrazinamide was begun, and the patient was discharged for outpatient follow-up. Cultures of the gastric mass subsequently grew *Mycobacterium tuberculosis* sensitive to isoniazid and rifampin. Two weeks after therapy was initiated, he was completely afebrile. After one month his epigastric pain had resolved and he had gained 7 kg. A CT scan at the time showed notable diminution in the size of the gastric mass to 2.5 by 2 by 2 cm. Another scan at three months showed a residual 1- by 1-cm thickening at the gastroesophageal junction.

Discussion

In the early 1900s, tuberculous involvement of the gastrointestinal tract due to pulmonary tuberculosis was a fairly common occurrence, especially in patients with far-advanced lung infection.[7,8] After the introduction of successful antituberculous regimens, the percentage of pulmonary tuberculosis cases with clinically evident secondary gastrointestinal involvement decreased from 38% to less than 5%.[7,9]

Gastrointestinal tuberculosis can occur in the absence of additional sites of infection. In the first half of the century, this form of the disease was due mainly to the ingestion of *Mycobacterium bovis* in infected milk. Bovine intestinal tuberculosis has now been essentially eradicated in countries with milk pasteurization and tuberculous testing of dairy herds.[7,8] Isolated gastrointestinal infection with *M tuberculosis*, however, remains a problem today, representing about 3% of all cases of tuberculosis and at least 50% of all cases of gastrointestinal tuberculosis.[7,8,10,11] Its incidence may actually be rising in recent years, especially in populations with immigrants from Third World countries and patients with the acquired immunodeficiency syndrome.[2,10-13] Only about 50% of these cases are diagnosed accurately, mainly because tuberculosis is often not considered in the diagnosis.[14]

There has been much debate regarding the origin of gas-

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